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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/072,767	02/07/2002	Brian Lee Batley	A0000403-01-JP	2919

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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	2

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/072,767	BATLEY ET AL	
	Examiner	Art Unit	
	Daniel Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-50 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-50 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Claims 1-50 are pending in the application.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Specification

The disclosure is objected to because of the following informalities:

Page 4, paragraph 2 of the disclosure describes a cell line comprising a reporter construct having an expressible reporter element (described in lines 1-7), which is *also* transfected with "...a yeast GAL4 binding element-driven luciferase reporter construct" (lines 20-21). The paragraph does not make sense in the context of the rest of the disclosure because it reads as though the cell line comprises two reporter constructs one of which is a luciferase reporter construct.

On page 4, line 32, a close parenthesis is missing.

On page 5, line 3, "reported vector" should be "reporter vector".

On page 8, line 17, "Luciferase" is misspelled.

Appropriate correction is required.

Claim Objections

Claims 1, 21, 29 and 49 objected to because of the following informalities:

In claims 1 and 29, it appears that the conjunction "and" should be inserted so that the claims read "...an expression vector encoding a gene for a VEGF receptor *and* detecting the presence of..." The claims do not make sense as written.

Claims 21 and 49 would make more sense if the conjunction "or" replaced "and" to clearly indicate that the cells, tissue, and tissue extracts can be used independently as well as in combination.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19 and 47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claims recite the limitation "biological fluids". The limitation is not described in the specification and the dependent claims provide only "plasma" and "cell culture media" as examples of biological fluids. The Revised Interim Guidelines state, "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus". (Column 2, page 71436). The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics (see MPEP 2163 (ii)). From the examples provided, the genus biological fluid encompasses at least any fluid obtained from a biological system or a fluid capable of sustaining a biological system. These examples are widely divergent and do not provide sufficient description to allow one of ordinary skill in the art ascertain the identifying characteristics of a biological fluid. Therefore, the disclosure does not reasonably convey to one of ordinary skill in the art that the applicants had the claimed invention in their possession at the time the application was filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25, 29 and 35-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 29 are drawn to a method comprising "a chimeric transactivatable vector". This description implies that this vector is activated in trans and makes the claim indefinite because the disclosure does not provide the circumstances or manner in which this particular vector (i.e. the vector comprising the phosphorylatable protein) is activated. In the context of the instant application, it would appear that the intention of the applicants is to describe the protein encoded by the vector (i.e. a chimeric *transactivator*), and the claims have been examined on the merits based on that assumption. This rejection can be traversed by amending the claims to read "chimeric transactivat*or* vector" when referring to the vector encoding the chimeric phosphorylatable protein, and amending the dependent claims to maintain correct antecedence.

Claims 1, 7, 14, 24, 25 and 35 are indefinite because they recite limitations without a preceding definite or indefinite article. For example, Claim 7, line 2 reads, "...encoded by chimeric transactivatable vector...". It is not clear whether the claim is drawn to *the* chimeric transactivatable vector of Claim 1 or to *a* transactivatable vector that could comprise the vector of claim 1 and other transactivatable vectors. The claims should be examined for missing articles and corrected to distinctly claim the subject matter that the applicant regards as the invention.

Claims 22 and 23 are drawn to a method wherein VEGF activity is detectable at an indicated concentration range. The claims are indefinite because it is not possible to express activity in units of concentration. In chemistry, concentration is defined as the amount of a physical component in a given volume. The method of Claim 1, from which the claims depend, is not limited to VEGF only, and without knowing the identity of the molecule responsible for the activity it is not possible to determine its concentration. In the interest of compact prosecution, the claims have been examined under the assumption that the applicants intended for the claims to be drawn to a method wherein VEGF activity is detectable at a *VEGF* concentration within the indicated ranges.

Claim 29 is drawn to a method comprising steps (a), (b), (c) and (d), wherein steps (a) and (b) are drawn to contacting a cell expressing VEGF with a candidate compound, step (c) is drawn to contacting a sample to be assayed for VEGF activity with a cell line comprising a heterologously expressed VEGF receptor and a reporter system for VEGF receptor activation, and detecting the presence of the expressed reporter element as a measure of VEGF activity; and step (d) is drawn to detecting expression of the reporter element, wherein expression of the reporter element indicates VEGF activity. It is not clear in the claim how steps (a) and (b) are related to steps (c) or (d) because neither (c) nor (d) contain a definite reference to the limitations of steps (a) and (b). In fact, the cell line of step (a), which expresses VEGF, is by necessity different from the cell line of step (c), which is intended to detect VEGF, because expression of VEGF in the cell line of step (c) would render the method inoperable. Step (b) is a process step that is indistinguishable from the process step contained in step (c) and is therefore either

redundant or insufficiently described. Likewise, it is unclear how step (d) is related to the method of step (c) because the step does not appear to be different from the detection method already recited in step (c). Finally, step (d) cannot be related to steps (a) or (b) because there is no antecedent for "the reporter element" in (a) or (b). In the interest of compact prosecution, the Claim will be examined under the assumption that the applicants intend the claim to read on a method for identifying compounds that affect VEGF-stimulated signaling wherein the VEGF produced by the cell line of step (a) is combined with the compound of step (b), and the cell line of step (c) is contacted with the resultant combination.

Claims 9 and 37 recite the limitation "promoting element" without indicating what the element will promote. This rejection can be traversed by amending the claim to read "*promoter* element", which is known in the relevant art to describe an element that promotes expression of a gene operably linked to said promoter element.

Claims 15 and 43 recite the limitation "said including contacting step" in line 1. There is insufficient antecedent basis for this limitation in the claim. This rejection can be traversed by amending the claims to read "said contacting step".

Claims 16 and 44 recite the limitation "transactivator" in line 2. There is insufficient antecedent basis for this limitation in the claim. This rejection can be traversed by amending Claims 1 and 29 as recommended above (page 5, second full paragraph).

Claim 42 recites the limitation "said contacting step" in line 1. The antecedent basis for this limitation is unclear because there are two distinct contacting steps (one in step (b) and one in step (c)) in Claim 29.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 26 is rejected under 35 U.S.C. 102(a) as being anticipated by Murta et al. (2000) *J Ocular Pharmacol and Ther* 16:383.

The claim is drawn to a method comprising the steps of: (a) providing a cell expressing FLK-1; (b) contacting the cell with a candidate compound; and (c) measuring VEGF receptor activity wherein altered VEGF receptor activity relative to a cell not contacted with the a candidate compound indicates that the candidate compound modulates VEGF receptor activity. Murta teaches a method comprising a cell expressing FLK-1 (see especially Figure 3), contacting the cell with a candidate compound (VEGF) and comparing Elk-1 phosphorylation, as an indicator of VEGF receptor activity, in cells contacted with VEGF and not contacted with VEGF (see especially Figure 4 and the caption thereto). The method taught by Murta is the same as the method taught in the instant application, therefore the limitations of the claim are met by Murta.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States

Claim 26 is rejected under 35 U.S.C. 102(b) as being anticipated by either of Wen et al (1999) *Biochem Biophys Res Commun* 258:713-721 or Ullrich et al. (1994; WO 94/11499).

The limitations of the claim are recited above. Wen teaches a method comprising a cell expressing FLK-1 (see especially Figure 6 and the caption thereto), contacting the cell with a candidate compound (VEGF) and comparing protein phosphorylation, as an indicator of VEGF receptor activity, in cells contacted with VEGF and not contacted with VEGF (see especially Figures 5 and 6 and the captions thereto). Ullrich teaches a method comprising "engineered cell lines which express the entire FLK-1 coding region... to screen and identify VEGF antagonists as well as agonists" (page 23, lines 31-34), wherein the ability of agents to mimic the effect of VEGF binding on signal transduction responses is used as an indicator of VEGF activity (see especially "5.3 USES OF THE Flk-1 RECEPTOR AND ENGINEERED CELL LINES"). The methods taught by Wen and Ullrich are the same as the method taught in the instant application, therefore the limitations of the claim are met by Wen and Ullrich.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-20, 22-24, 26-48 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ullrich in view of Hexdall (1999) *Strategies* volume 12, issue 2 and in further view of Shibuya (1999) *International Congress Series* 1175:25-33.

Claim 1 is drawn to a method for determining VEGF activity in a sample comprising the steps of: contacting a sample to be assayed with a stable cell line comprising cells transfected with a reporter having an expressible reporter element and a DNA binding site disposed adjacent thereto, a chimeric transactivat[or] vector comprising a gene encoding a phosphorylatable protein and a DNA binding domain which binds to the DNA binding site, and an expression vector encoding a gene for a VEGF receptor [and] detecting the presence of [the] expressed reporter element wherein expression of the reporter element indicates VEGF activity.

The limitations of Claim 26 are recited above. Claim 27 is drawn to the method of Claim 26 wherein the cell further comprises a reporter vector having an expressible reporter element and a DNA binding site disposed adjacent thereto, and a chimeric transactivator vector comprising a gene encoding a phosphorylatable protein and a DNA binding domain, which specifically binds to the DNA binding site. Claim 28 is drawn to the method of 27 wherein said measuring step is further defined as comparing levels of the expressed reporter element from the cell contacted with the candidate compound relative to a cell not contacted with the candidate compound

As indicated above, Claim 29 and those claims depending from Claim 29 are being examined as a method for identifying compounds that affect VEGF-stimulated signaling wherein the VLGF produced by the cell line of step (a) is combined with the compound of step (b), and the cell line of step (c) is contacted with the resultant combination.

Ullrich teaches a method of screening samples for VEGF activity, comprising contacting a cell line comprising an expression vector encoding the entire FLK-1 coding region with said sample and measuring the effect on signal transduction responses in the FLK-1 expressing cells; a method for identifying antagonists of VEGF-stimulated signaling wherein cells are contacted with VEGF and a candidate compound (see especially "5.3 USES OF THE Flk-1 RECEPTOR AND ENGINEERED CELL LINES"); and obtaining VEGF from media conditioned by a VEGF expressing cell line (see especially page 39, lines 21-29). Ullrich does not teach a cell line comprising an expressible reporter element and a DNA binding site disposed adjacent thereto, a chimeric transactivator vector comprising a gene encoding a phosphorylatable protein and a DNA biding domain that binds to the DNA binding site in addition to an expression vector encoding a VEGF receptor.

Hexdall teaches a stable cell line transfected with a reporter having an expressible reporter element and a DNA binding site disposed adjacent thereto, a chimeric transactivator vector comprising a gene encoding a phosphorylatable protein and a DNA biding domain that binds to the DNA binding site, and the use of said stable cell lines for high-throughput drug screening of receptors that activate the MAP kinase pathway. Shibuya teaches activation of the MAP kinase pathway by FLK-1. In view of the teaching of Shibuya, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the cell line of Hexdall according to the method of Ullrich to determine VEGF agonist and antagonist activity in a sample. Motivation to combine these teachings comes from Ullrich, who states the value of pharmaceutical reagents capable of activating or inhibiting VEGF and that cell lines--including HeLa cells (page 20, line 2)--engineered to express Flk-1 could be used to screen VEGF agonists

and antagonists (see page 3, paragraph 2), and from Hexdall who states that their cell line "... offer[s] ... improved performance for adaptation to high-throughput applications..." and that "By performing simple luciferase assays, researchers can directly evaluate the effects of extracellular stimuli on signaling pathways" (Page 2, second full paragraph). One would have a reasonable expectation of success in combining these teachings in view of FLK-1 stimulated activation of MAP kinase, taught by Shibuya, and phosphorylation of ELK-1, taught by Murta.

Claims 2-20, 24 and 30-48 further limit Claims 1 and 26-29. Hexdall teaches the reporter vector further comprising a GAL4 binding element of Claims 2 and 30; the reporter vector comprising a gene encoding for a detectable product of Claims 3 and 31; the detectable product comprising luciferase of Claims 4 and 32; the gene encoding the detectable product operably linked to a promoter element of Claims 5 and 33; the promoter element comprising a TATA box of Claims 6 and 34; the phosphorylatable protein encoded by [the] chimeric transactivat[or] vector phosphorylated by MAPK of Claims 7 and 35; the phosphorylatable protein comprising ELK-1 of Claims 8 and 36; the gene encoding the phosphorylatable protein operably linked to a promot[er] element of Claims 9 and 37; the stable cell line comprising HeLa cells of Claims 13 and 41; expression of the transactivator vector to produce a chimeric product comprising the phosphorylatable protein and DNA binding domain of Claims16 and 44; the step of phosphorylating the chimeric product with activated MAPK of Claims17 and 45; the step of binding the phosphorylated chimeric product to the DNA binding site of the reporter vector, wherein expression of the expressible reporter element is activated of Claims 18 and 46; and incubating the sample with the stable cell line for a period of time ranging from approximately 4 hours to approximately 24 hours of Claim 24 (see especially Figure 4 and the caption thereto; see

also Xu (1997) *Strategies* 10:1-3, cited in Hexdall, for a more complete description of the constructs comprised in the cell line of Hexdall).

Ullrich teaches the VEGF receptor comprising FLK-1 of Claims 10, 12, 38 and 40; the VEGF receptor-encoding gene operably linked to a promoter element of Claims 11 and 39, and the contacting step comprising binding VEGF present in the sample with the expressed VEGF receptor of Claims 14 and 42. In addition, Ullrich teaches a method comprising contacting cells expressing FLK-1 with monoclonal or polyclonal antibodies, in which case the sample would comprise the cell culture media or plasma of claims 19, 20, 47 and 48. As described above, Shibuya teaches the contacting step comprising activating MAPK with the expressed VEGF receptor of Claims 15 and 43.

Finally, Claim 50 is drawn to a stable cell line transfected with a reporter vector encoding a luciferase gene and a GAL4 DNA binding site; a chimeric transactivator vector encoding for an FLK-1/GAL4 DNA binding domain fusion protein; and a vector encoding for VEGF receptor FLK-1. As described above, Ullrich and Hexdall teach all of the limitations of the claim.

Claims 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ullrich in view of Hexdall as applied to Claim 1 above, and further in view of Wen. As stated above, the claims are examined with the assumption that the applicants intend that they be drawn to the method of Claim 1 wherein VEGF activity is detectable at a VEGF concentration > 1 mg/ml, Claim 22, or in a concentration range from approximately 1 ng/mL to approximately 200 ng/mL, Claim 23. Wen teaches activation of Flk-1, as indicated by protein tyrosine phosphorylation, at a

VEGF concentration of 50 ng/mL. Therefore it would be obvious to one of ordinary skill in the art at the time the invention was made that the cell line produced by combining the teachings of Ullrich and Hexdall would be able to detect VEGF activity at a VEGF concentration in the range of 1-200 ng/mL and at a VEGF concentration >1 mg/ml.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
May 22, 2002

JAMES KETTER
PRIMARY EXAMINER